CombiGlide 2.5

Quick Start Guide

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Contents

Document Conventions

In addition to the use of italics for names of documents, the font conventions that are used in this document are summarized in the table below.

Font	Example	Use
Sans serif	Project Table	Names of GUI features, such as panels, menus, menu items, buttons, and labels
Monospace	`$SCHRODINGER/maestro`	File names, directory names, commands, environment variables, and screen output
Italic	*filename*	Text that the user must replace with a value
Sans serif uppercase	CTRL+H	Keyboard keys

Links to other locations in the current document or to other PDF documents are colored like this: Document Conventions.

In descriptions of command syntax, the following UNIX conventions are used: braces `{ }` enclose a choice of required items, square brackets `[ ]` enclose optional items, and the bar symbol | separates items in a list from which one item must be chosen. Lines of command syntax that wrap should be interpreted as a single command.

File name, path, and environment variable syntax is generally given with the UNIX conventions. To obtain the Windows conventions, replace the forward slash / with the backslash \ in path or directory names, and replace the $ at the beginning of an environment variable with a % at each end. For example, `$SCHRODINGER/maestro` becomes `%SCHRODINGER%\maestro`.

In this document, to *type* text means to type the required text in the specified location, and to *enter* text means to type the required text, then press the ENTER key.

References to literature sources are given in square brackets, like this: [10].

Overview

CombiGlide employs combinatorial technology for lead identification and optimization. It presents three distinct workflows:

1. The Core Hopping workflow—Starting with a lead compound in a well-docked pose, find alternative cores that bind well to a receptor of interest.
2. The Virtual Combinatorial Screening workflow—Use our proprietary technology to explore an extremely large combinatorial space in order to find side chains for a core chemical scaffold that will optimize binding to a receptor of interest.
3. The Enumerate and Dock workflow—Enumerate a combinatorial library; dock it, analyze and evaluate the results. This is most useful for relatively small libraries.

All of these can be used either as a prelude to combinatorial design or as a means of conventional lead discovery and optimization. See the *CombiGlide User Manual* for details.

This document provides several tutorial examples.

Chapter 2 provides a tutorial example of the Core Hopping workflow. The docking step takes about 30 minutes on a 2 GHz x86 processor.

Chapter 3 provides a tutorial example of the Virtual Combinatorial Screening workflow. The center of the tutorial—the docking step—takes about 3 hours on a 2 GHz Pentium processor, so you should plan the resources you need for the tutorial accordingly.

Chapter 4 provides a tutorial example of the analysis of the results of a virtual combinatorial screening run in terms of the distribution of chemical features and the enrichment of actives. This examples uses files taken from a run as input, and does not involve significant processing time.

1.1 Preparing for the Exercises

To run the tutorials, you must have access to an installed version of Maestro 9.0, CombiGlide 2.5, LigPrep 2.3, and QikProp 3.2. For installation instructions, see the *Installation Guide*. Before you begin, you must create a working directory, and copy files from the CombiGlide distribution into this directory.

To set up the working directory:

1. Set the `SCHRODINGER` environment variable to the directory in which CombiGlide is installed:

   csh/tcsh: `setenv SCHRODINGER` *installation_path*

   sh/bash/ksh: `export SCHRODINGER=`*installation_path*

2. Change to a directory in which you have write permission.
3. Create a working directory for the tutorial:

   `mkdir` *workdir*

4. Change to the working directory:

   `cd` *workdir*

5. Copy all the files for the tutorial to this directory:

   `cp -r $SCHRODINGER/combiglide-v`*version*`/tutorial/* .`

   Here, *version* is the 5-digit version number of the CombiGlide distribution.

Core Hopping Tutorial

In these exercises protocore docking is used to find substitute cores for a known ligand, that of the protein 1nde. The object of core hopping is to identify promising lead compounds, which exhibit good GlideScores and possess fewer rotatable bonds than the known ligand.

Core hopping is described in Chapter 2 of the *CombiGlide User Manual*. This tutorial assumes that you have read the discussion of core hopping in that chapter and that you are familiar with the way in which we use the terms template, core, protocore and linkers. It also assumes familiarity with basic Maestro operations. If you are not familiar with Maestro, see the *Maestro Tutorial* for exercises in Maestro operations.

2.1 Starting the Exercises

The exercises in this chapter use Maestro to set up and run jobs. To start the exercises, you need to start Maestro and save the project as a named project. If you have not created a working directory and copied the tutorial files, do so now using the instructions in Section 1.1 on page 1.

1. Change to your working directory:

   `cd` *workdir*

2. Extract the tutorial files from the archive:

   ```
   tar xzf core_hopping.tar.gz
   ```

   The files are extracted into the subdirectory `ch_tutorial_files`.

3. Change to the tutorial subdirectory:

   ```
   cd ch_tutorial_files
   ```

If Maestro is not running, follow the next two steps.

1. Start Maestro with the command:

   ```
   $SCHRODINGER/maestro &
   ```

   The Maestro main window is displayed.

2. Choose Save As from the Project menu and save your project as `ch_tutorial`.

   All the results are saved in the project, so you must save the project if you want to exit Maestro and resume the tutorial or view the results later.

If you already have a Maestro session, follow the next two steps:

1. From the Maestro menu, choose Change Directory, and navigate to the tutorial subdirectory.
2. From the Project menu, choose New, and save your project as `ch_tutorial`.

2.2 Importing the Receptor and Template

In this exercise, the receptor and the template that is to be used for core hopping are imported into Maestro.

1. Click the Import structures button in the Maestro toolbar.

   The Import panel opens.
2. Navigate to the `1nde` directory.
3. Select both the `1nde_recep.mae` and the `ligand.mae` files, and click Open.

   Both structures are imported and added to the Project Table.
4. If the Project Table panel is not open, click Open/Close project table in the main window.

   
5. In the Project Table, include 1nde_ligand in the Workspace by clicking the In column.

   The ligand is visible in the Workspace.
6. Rotate the ligand in the Workspace by clicking the Rotate around Y axis by 90 degrees toolbar button:

The ligand should appear as shown in Figure 2.1. This is the structure of the 1nde ligand, which we will use as a template for core hopping.

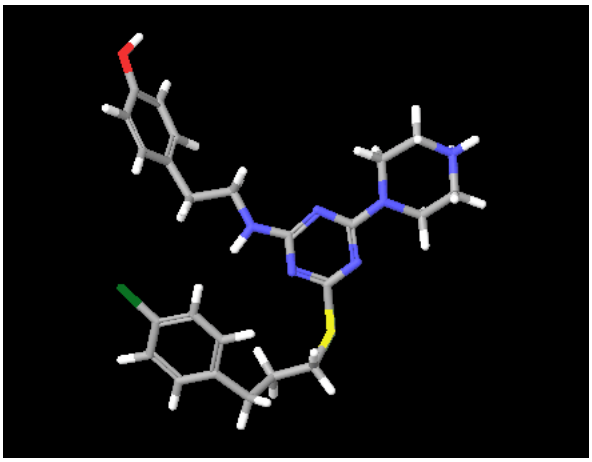


Figure 2.1. The 1nde ligand.

2.3 Selecting the Protocores for Docking

1. From the Applications menu, choose CombiGlide > Core Hopping > Protocore Docking.

   The Protocore Docking panel opens.

2. Ensure that File is chosen in the Use structures from option menu.

3. To specify the file, click Browse.

   A file selector panel opens, displaying the files in the `ch_tutorial_files` directory.

4. Select `tutorial-2_linkers.mae` and click Open.

   The file selector closes, and the file name is displayed in the File name text box.

   In this file there are a small number of protocore-containing molecules, already prepared with two linkers in each attachment bond.

5. Ensure that the Task option selected is Align protocores and dock molecules.

This is the default choice, which requests the running of a two-stage core-hopping job. In the first stage (Alignment), the protocores are aligned to the 1nde ligand in an effort to find attachment bonds on the protocores that align well with attachment bonds on the template (yet to be selected). In the second stage (Docking), the well aligned cores that result have the side chains from the template molecule added to the newly identified attachment bonds, and these molecules are docked and sorted as described below. At the end of this process, we expect the best molecules to appear near the top of the sorted list.

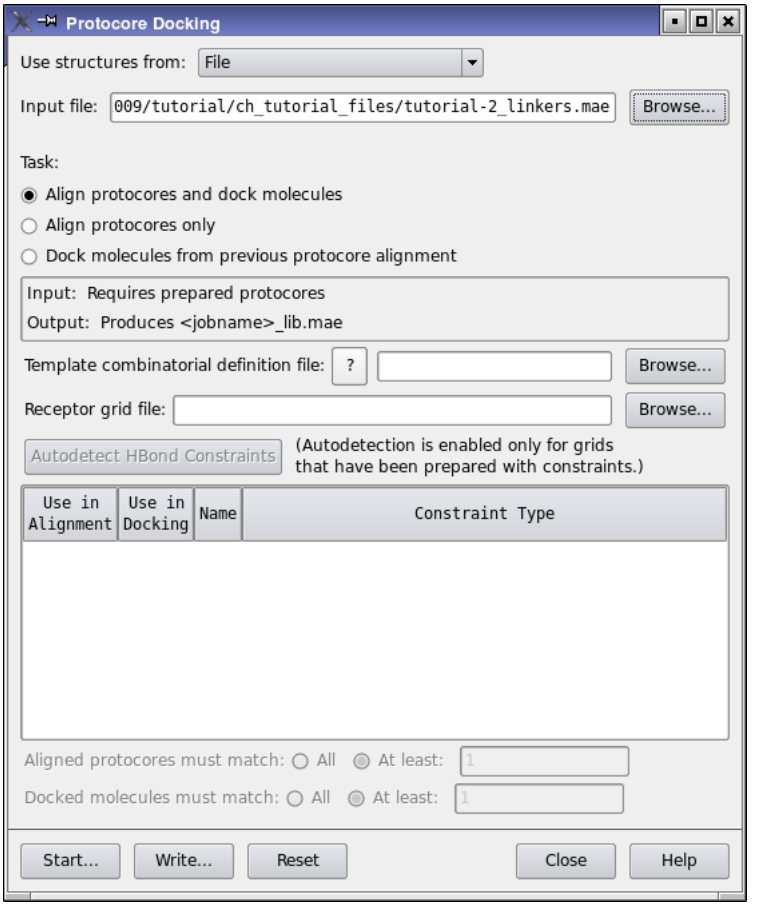


Figure 2.2. The Protocore Docking panel.

2.4 Creating a Combinatorial Definition File

The next thing needed is a combinatorial definition file. This file contains a core and a list of attachments (and possibly additional information that is useful for combinatorial screening, but not for core hopping). Here, you will prepare the minimal combinatorial definition file required for a core-hopping exercise starting with the ligand that you imported.

1. Click the question mark (?) button next to the text Template combinatorial definition file.

   The Instructions dialog box opens (see Figure 2.3). This dialog box provides instructions for preparing a combinatorial definition file.

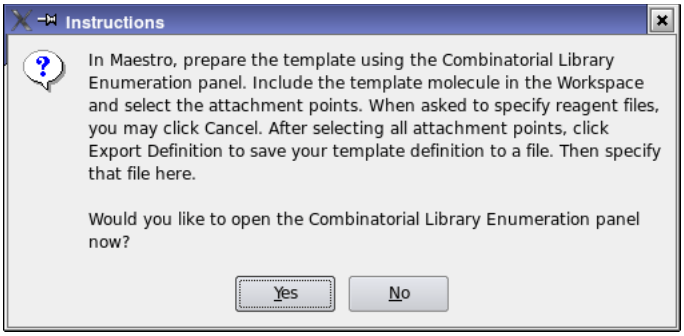


Figure 2.3. The Instructions dialog box.

2. Click Yes to open the Combinatorial Library Enumeration panel.

   The Combinatorial Library Enumeration panel opens, with the Pick molecule option selected.

3. Click on any atom in the Workspace.

   The Core Molecule dialog box is displayed. This dialog box allows you to provide a title for the core molecule. You can rename the starting molecule anything you choose, but for this exercise, the default name of core will be used.

4. Click OK.

5. The dialog box closes, and the controls in the Combinatorial Library Enumeration panel are enabled. Beneath the empty Attachments table, the Pick option in the Pick to define an attachment section is selected. This option allows you to pick attachment bonds.

The next task is to select three attachment bonds to define the boundary between the core that we want to replace and the side chains. In the template molecule, there are a total of 10 rotatable bonds. Although some of them have some degree of sp^2 character and thus are not fully flexible, we are going to be ambitious and try to replace the entire center portion of the molecule, up to the peripheral rings, with a substitute core. The hope is that this will result in a more rigid structure. To attempt this task, the protocores have been prepared with two linkers. Because the rigid cores within the protocore file are small, it is unlikely that good alignment with the large central portion of the 1nde ligand will be achieved without linkers. The alignment process uses only those portions of the linker chains that it needs to. Of course, linkers add flexibility beyond that of a rigid core, but the goal is to find a system that is more rigid overall than the template.

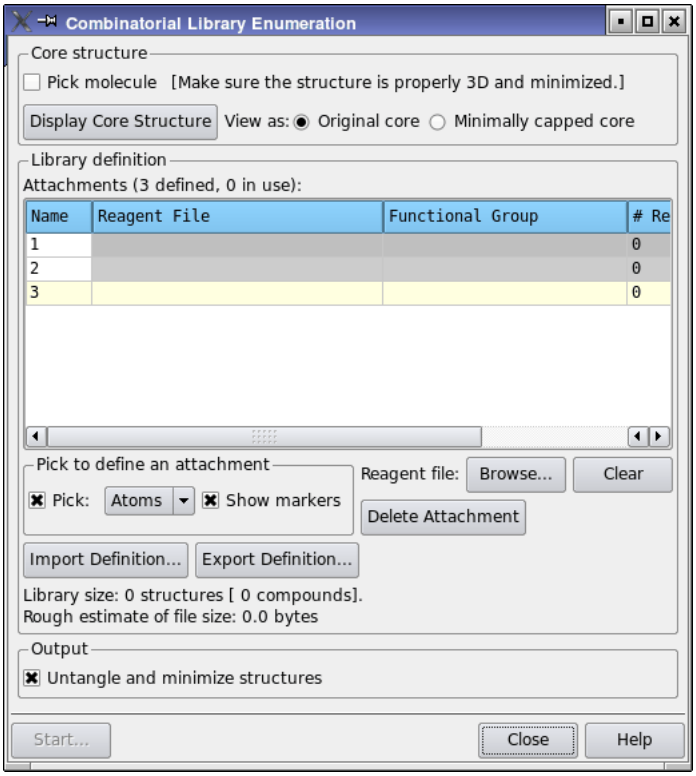


Figure 2.4. The Combinatorial Library Enumeration panel.

Each attachment bond is defined by picking two atoms: first the atom closer to the core and then the atom closer to the side chain. The order is important because it defines the side chain and, when all attachments have been defined, the core.

6. Pick the carbon atom that is attached to the para-phenolic ring, then pick the ring atom it is bonded to.

   An arrow is displayed, pointing toward the ring (see Figure 2.5). The Select Reagent File file selector is also displayed. Since reagent files are not used for core hopping, you can dismiss this file selector.

7. Click Cancel in the Select Reagent File file selector.

8. Pick the carbon atom that is attached to the para-chlorophenyl ring, then pick the ring atom it is bonded to.

9. Click Cancel in the Select Reagent File dialog box.

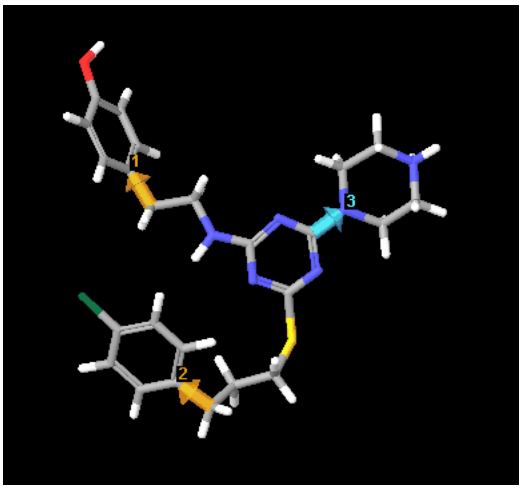


Figure 2.5. The 1nde ligand showing the attachment positions.

10. Pick the carbon atom that is attached to the piperazine ring (this atom is in the central ring), then pick the ring atom it is bonded to.

    When you have finished, the Workspace should look like Figure 2.5.

11. Click Cancel in the Select Reagent File dialog box.

The next task is to save the combinatorial definition file.

12. Click Export Definition.

    The Export Definition File file selector opens.

13. In the File name text box, type `1nde_ligand`.

14. Click Save.

    A file named `1nde_ligand-comdef.tar.gz` is written, which is the desired combinatorial definition file.

15. Close the Combinatorial Library Enumeration panel.

2.5 Setting Up and Running the Protocore Docking Job

In this exercise you will finish making the settings for the protocore docking job and run it.

1. In the Protocore Docking panel, click the Browse button for the Template combinatorial definition file.

   A file selector opens.

2. Select the file `1nde_ligand-comdef.tar.gz` (created in the previous exercise) and click Open.

   The file name is displayed in the Template combinatorial definition file text box.

3. Click the Browse button for the Receptor grid file.

   A file selector opens.

4. Navigate to the `1nde` directory, select the file `1nde.grd`, then click Open.

   The file name is displayed in the Receptor grid file text box.

   When receptor grids are prepared with constraints, the constraints to use can be selected in the bottom half of the panel. This tutorial exercise does not use constraints.

5. Click Start.

6. The Start dialog box opens. The default settings are acceptable for this job. You can select a different host if you wish. The job should take about 30 minutes.

7. Click Start.

8. Close the Protocore Docking panel.

2.6 Visualizing the Results

After the job finishes, the results are incorporated into the project and appear in the Project Table. The visualization of the results will be done with the Core Hopping Visualization panel.

1. From the Applications menu, choose CombiGlide > Core Hopping > Core Hopping Visualization.

   The Core Hopping Visualization panel opens.

2. If the Project Table panel is not already open, click the Open/Close Project Table button on the main toolbar.

3. Select the template molecule entry (1nde_ligand) in the Project Table.

   This entry should be the only entry selected. If it is not, click in the Row column for the entry.

4. Click Visualize Template Structure in the Core Hopping Visualization panel.

   A dialog box opens, requesting that only the template is displayed in the Workspace.

5. Click Select Template in the dialog box.

   The dialog box closes, the template is displayed in the Workspace with pink carbons, and the Visualize Receptor button becomes available in the Core Hopping Visualization panel.

6. Select only the receptor (1nde_recep) in the Project Table.

7. Click Visualize Receptor in the Core Hopping Visualization panel.

8. Click Select Receptor in the panel that is displayed.

   The panel closes. A surface representation of the receptor binding site is created and displayed in the Workspace along with the receptor in ribbon representation, and the Surface Table panel opens.

   The surface is opaque. The next few steps will make it semitransparent.

9. In the Manage Surfaces panel, click Display Options.

   The Display Options dialog box opens.

10. Under Transparency, adjust the Back surface transparency to about 65%, and click OK.

    The front surface transparency is adjusted as well because Adjust together is selected. The Workspace should look as shown in Figure 2.6.

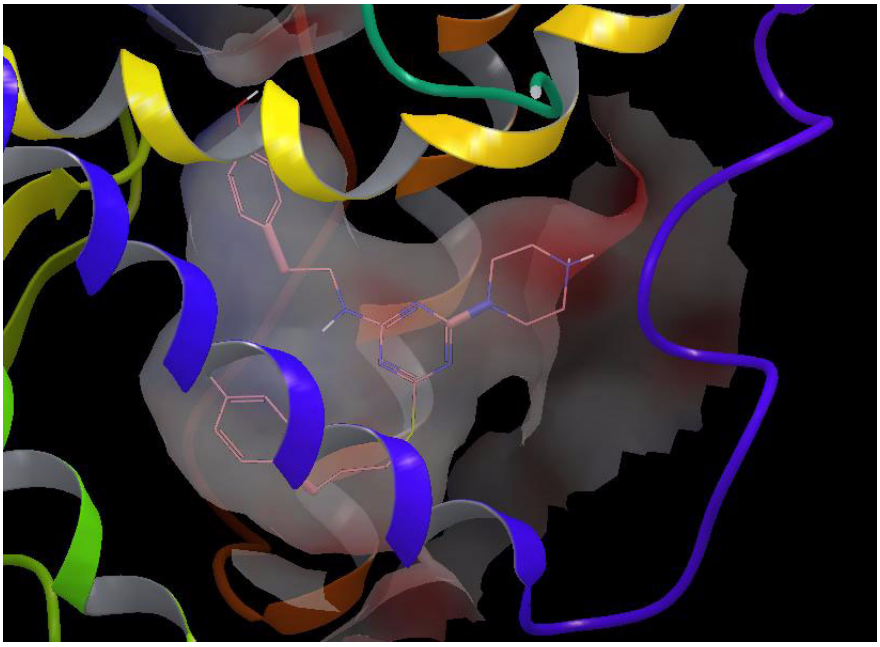


Figure 2.6. The 1nde receptor and ligand with the semitransparent receptor surface.

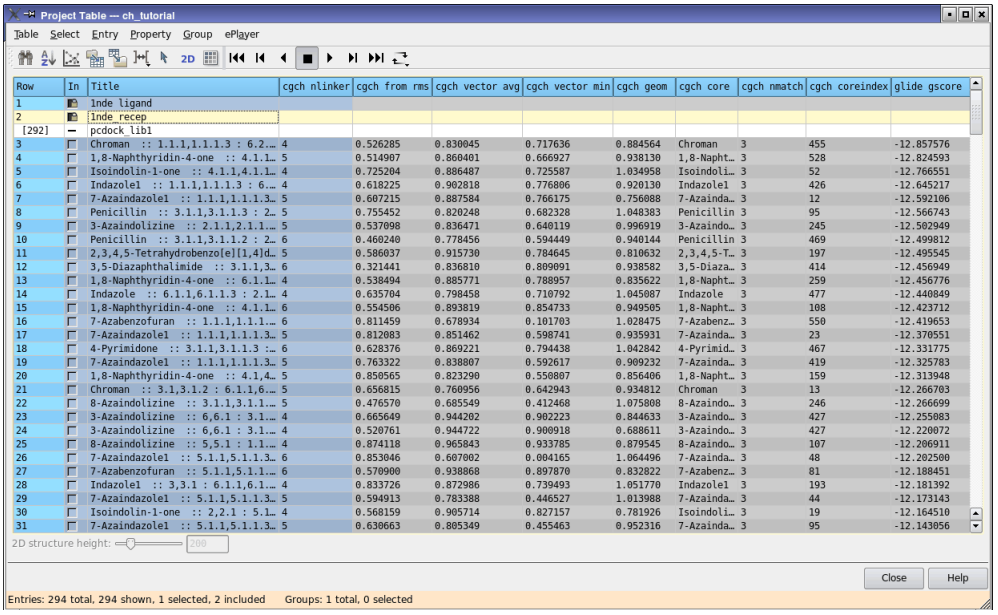
11. Close the Manage Surfaces panel (but leave the Core Hopping Visualization panel open).

The Workspace is now set up for visualization of the results of the protocore docking. The new structures were incorporated in a group called pcdock_lib1. You can include one or more of the structures in the Workspace to view them together with the template in the binding pocket.

The titles of these structures are composed of two parts: a core name (which also appears in the cgch core property), then a double colon ('::'), followed by some numbers, some with one or more decimal points. The core name is the title of a structure in the input protocore file (`tutorial-2_linkers.mae`, in this case). The remaining part of the title consists of a code that describes which bonds from the input protocore molecule were aligned to the template's attachment bonds. Exactly what these numbers mean is not important: what is important is that if the same core aligns to the template in several different ways, this part of the title will be different.

While the Core Hopping Visualization panel remains open, the columns displayed in the Project Table are limited to those properties deemed useful for examining core-hopping results. We will focus on three properties: cgch nlinker, cgch geom, glide gscore, and cgch nmatch.

The structures in the Project Table are sorted by the glide gscore (GlideScore) in ascending order. Thus, the molecules that docked with the best GlideScore appear at the top. The structures at the top of the list are the best core-hopped structures, based on GlideScore.



Row	In	Title	cgch nlinker	cgch from rms	cgch vector avg	cgch vector min	cgch geom	cgch core	cgch nmatch	cgch coreindex	glide gscore
1		1nde_ligand									
2		1nde_recep									
[292]		pcdock_lib1									
3		Chroman :: 1.1.1,1.1.1.3 : 6.2…	4	0.526285	0.830045	0.717636	0.884564	Chroman	3	455	-12.857576
4		1,8-Naphthyridin-4-one :: 4.1.1…	5	0.514907	0.860401	0.666927	0.938130	1,8-Naphth…	3	528	-12.824593
5		Isoindolin-1-one :: 4.1.1,4.1.1…	4	0.725204	0.886487	0.725587	1.034958	Isoindolin…	3	52	-12.766551
6		Indazole1 :: 1.1.1,1.1.1.3 : 6.…	4	0.618225	0.902818	0.776806	0.920130	Indazole1	3	426	-12.645217
7		7-Azaindazole1 :: 1.1.1,1.1.1.3…	5	0.607215	0.887584	0.766175	0.756088	7-Azainda…	3	12	-12.592106
8		Penicillin :: 3.1.1,3.1.1.3 : 2…	5	0.755452	0.820248	0.682328	1.048383	Penicillin	3	95	-12.566743
9		3-Azaindolizine :: 2.1.1,2.1.1.…	5	0.537098	0.836471	0.640119	0.996919	3-Azaindo…	3	245	-12.502949
10		Penicillin :: 3.1.1,3.1.1.2 : 2…	6	0.460240	0.778456	0.594449	0.940144	Penicillin	3	469	-12.499812
11		2,3,4,5-Tetrahydrobenzo[e][1,4]d…	5	0.586037	0.915730	0.784645	0.810632	2,3,4,5-T…	3	197	-12.495545
12		3,5-Diazaphthalimide :: 3.1.1,3…	6	0.321441	0.836810	0.809091	0.938582	3,5-Diaza…	3	414	-12.456949
13		1,8-Naphthyridin-4-one :: 6.1.1…	4	0.538494	0.885771	0.788957	0.835622	1,8-Naphth…	3	259	-12.456776
14		Indazole :: 6.1.1,6.1.1.3 : 2.1…	4	0.635704	0.798458	0.710792	1.045087	Indazole	3	477	-12.440849
15		1,8-Naphthyridin-4-one :: 4.1.1…	6	0.554506	0.893819	0.854733	0.949505	1,8-Naphth…	3	108	-12.423712
16		7-Azabenzofuran :: 1.1.1,1.1.1.…	6	0.811459	0.678934	0.101703	1.028475	7-Azabenz…	3	550	-12.419653
17		7-Azaindazole1 :: 1.1.1,1.1.1.3…	5	0.812083	0.851462	0.598741	0.935931	7-Azainda…	3	23	-12.370551
18		4-Pyrimidone :: 3.1.1,3.1.1.3 :…	6	0.628376	0.869221	0.794438	1.042842	4-Pyrimid…	3	467	-12.331775
19		7-Azaindazole1 :: 1.1.1,1.1.1.3…	5	0.763322	0.838807	0.592617	0.909232	7-Azainda…	3	419	-12.325783
20		1,8-Naphthyridin-4-one :: 4.1,4…	5	0.850565	0.823290	0.550807	0.856406	1,8-Naphth…	3	159	-12.313948
21		Chroman :: 3.1,3.1.2 : 6.1.1,6.…	5	0.656815	0.760956	0.642943	0.934812	Chroman	3	13	-12.266703
22		8-Azaindolizine :: 3.1.1,3.1.1.…	5	0.476570	0.685549	0.412468	1.075808	8-Azaindo…	3	246	-12.266699
23		3-Azaindolizine :: 6,6.1 : 3.1.…	4	0.665649	0.944202	0.902223	0.844633	3-Azaindo…	3	427	-12.255083
24		3-Azaindolizine :: 6,6.1 : 3.1.…	4	0.520761	0.944722	0.900918	0.688611	3-Azaindo…	3	427	-12.220072
25		8-Azaindolizine :: 5,5.1 : 1.1.…	4	0.874118	0.965843	0.933785	0.879545	8-Azaindo…	3	107	-12.206911
26		7-Azaindazole1 :: 5.1.1,5.1.1.3…	6	0.853046	0.607002	0.004165	1.064496	7-Azainda…	3	48	-12.202500
27		7-Azabenzofuran :: 5.1.1,5.1.1.…	6	0.570900	0.938868	0.897870	0.832822	7-Azabenz…	3	81	-12.188451
28		Indazole1 :: 3,3.1 : 6.1.1,6.1.…	4	0.833726	0.872986	0.739493	1.051770	Indazole1	3	193	-12.181392
29		7-Azaindazole1 :: 5.1.1,5.1.1.3…	5	0.594913	0.783388	0.446527	1.013988	7-Azainda…	3	44	-12.173143
30		Isoindolin-1-one :: 2,2.1 : 5.1…	4	0.568159	0.905714	0.827157	0.781926	Isoindolin…	3	19	-12.164510
31		7-Azaindazole1 :: 5.1.1,5.1.1.3…	5	0.630663	0.805349	0.455463	0.952316	7-Azainda…	3	95	-12.143056

Figure 2.7. The Project Table panel, set up for visualization and displaying the core-hopping properties.

The cgch nmatch property is the number of attachment bonds on the protocore that aligned to the template. This number is always the minimum of the number of attachment bonds defined in the combinatorial definition file (three in this case) and the number of possible attachment bonds on the protocore. If you scroll down to the bottom of the Project Table, you will see several molecules whose value of cgch nmatch is 2, rather than 3. These are matches to protocores that had only two attachment bonds. They are clearly less interesting than the structures that were able to match at all three positions on the template. Because they contain only two side chains from the template, they are not able to make excellent contact with the receptor, and thus their GlideScores are low.

The cgch nlinker property is the total number of methylene groups that were used as linkers in the current match. Core hopping, when linkers are in use, uses only up to the number of linkers present; it might not always need all linkers, and when it does not, chch nlinker is less than the maximum. The maximum here is six, two in each of the three positions on the template. Each methylene group contributes an additional rotatable bond to the total number of rotatable bonds in the system. In the absence of linkers, there would be as many rotatable bonds as there are attachments (assuming rigid substituted core and originally defined side chains). So, for results that matched the template at all three positions, the total number of rotatable bonds associated with the linkers is 3 +N, where N is the number of linkers that were used. Since it is better to avoid rotatable bonds when possible, it is better to focus on cores that required fewer linkers, while still achieving a high GlideScore, when considering possible candidate molecules for further development.

We already saw that the original template molecule had ten rotatable bonds. A molecule with four linkers would have seven rotatable bonds, a molecule with five linkers would have eight, and a molecule with six linkers (the maximum possible here) would have nine, assuming that the side chains and the new central region (i.e., exclusive of linkers) are rigid. In the top-ranking structures by GlideScore, we can see values of chch nlinker ranging from 4 to 6. Other things being equal, one would prefer structures with fewer linkers; however, the structures shown demonstrate that many structures exhibiting excellent GlideScores were found that have fewer rotatable bonds than the number in the template.

Finally, we consider the cgch geom property. This is a measure of how well the attachment bonds of the protocore aligned to the corresponding attachment bonds of the template following the alignment stage. The measure is based on atomic RMSD, and includes the linkers. It is used to exclude matches that align poorly in the first (Alignment) stage from being processed through the second (Docking) stage. Following docking, however, the alignment changes, since the aligned protocore (with its linkers and side chains added) moves during docking.

Virtual Combinatorial Screening Tutorial

This chapter takes you through the use of CombiGlide for focused library design, including reagent preparation and combinatorial screening. The example used in this tutorial is a pyrazole library, which is designed to generate inhibitors of p38 MAP kinase. The synthetic approach for these compounds is described in Figure 3.1.

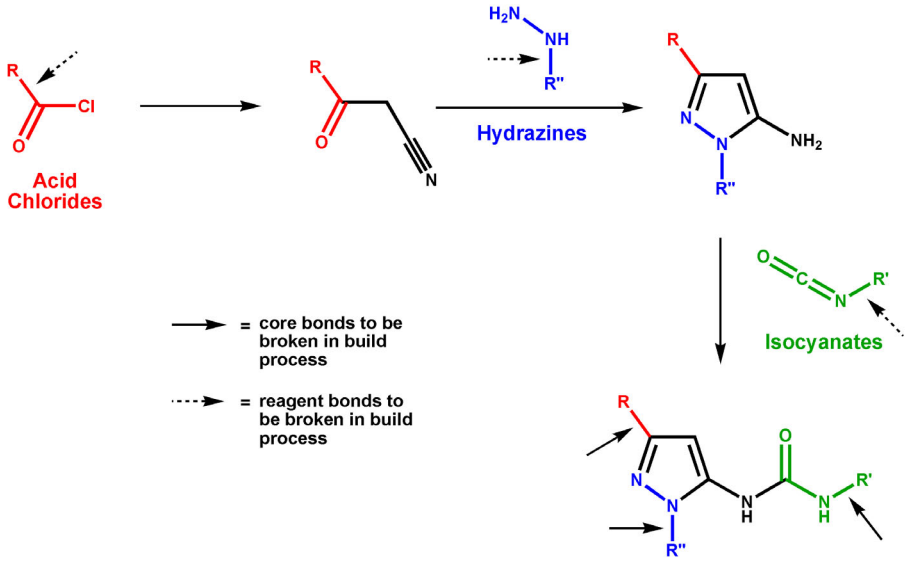


Figure 3.1. Synthetic route to pyrazole library.

The *core* is the structural element that is constant throughout the library. In the pyrazole example, the core is the structure given in Figure 3.2 minus the R, R', and R" groups.

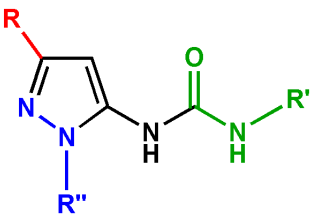


Figure 3.2. Core structure for pyrazole library design.

CombiGlide builds library members by adding the R, R', and R" groups from the reagents to the core structure. In the first part of the CombiGlide workflow, you provide a 3D, minimized structure of a molecule that contains this core, define the points at which the R, R', and R" groups are to be attached, and associate a set of reagents with each attachment point. You then select a receptor and set up parameters for docking with Glide. CombiGlide performs a series of docking calculations to determine a reduced set of reagents that is likely to contain the best candidates for the chosen receptor. In the final stage, you can narrow the library down to a small set, using various strategies for selection of the "best" reagents, then generate the library.

3.1 Starting the Exercises

The exercises in this chapter use Maestro to set up and run jobs. To start the exercises, you need to start Maestro, unpack the tutorial files, and save the project as a named project. If you have not created a working directory and copied the tutorial files, do so now using the instructions in Section 1.1 on page 1.

1. Change to your working directory and create a subdirectory named `cg_tutorial`:

   ```
   cd workdir
   mkdir cg_tutorial
   ```

2. Change to this new subdirectory:

   ```
   cd cg_tutorial
   ```

3. Extract the tutorial files from the archive you copied earlier:

   ```
   tar xzf ../comb_screening.tar.gz
   ```

If Maestro is not running, follow the next two steps.

4. Start Maestro with the command:

   ```
   $SCHRODINGER/maestro &
   ```

   The Maestro main window is displayed.

5. Choose Save As from the Project menu and save your project as `cg_tutorial`.

   All the results are saved in the project, so you must save the project if you want to exit Maestro and resume the tutorial or view the results later.

If you already have a Maestro session, follow the next two steps:

1. From the Maestro menu, choose Change Directory, and navigate to the tutorial subdirectory.
2. From the Project menu, choose New, and save your project as `cg_tutorial`.

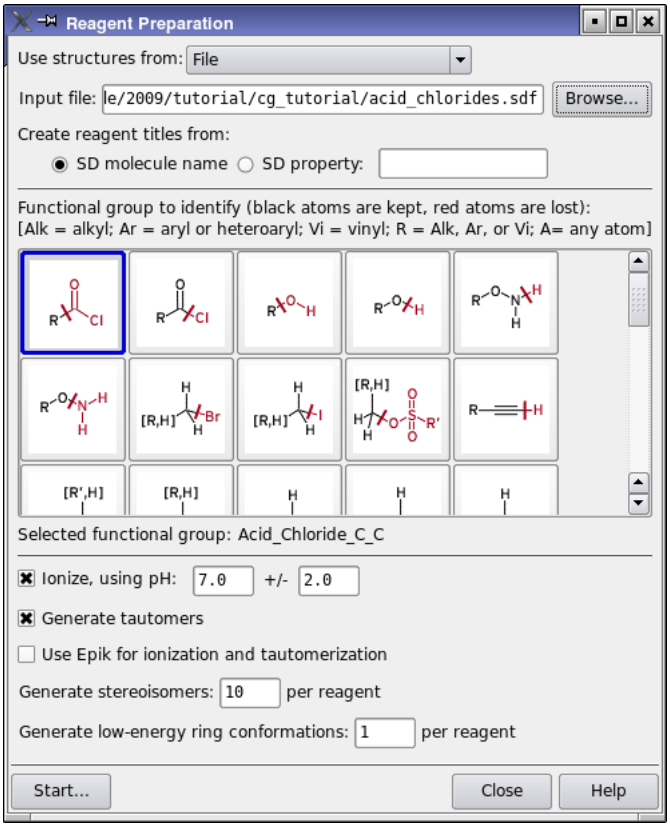


Figure 3.3. The Reagent Preparation panel.

3.2 Preparing the Reagents

The structures of the reagents that you want to use are often 2D structures. CombiGlide converts these structures to all-atom 3D structures suitable for the docking stage of the process, using LigPrep. The information needed to identify the fragment that will be added to the core is also added during reagent preparation. In this exercise, you will prepare the three reagent files needed to evaluate the pyrazole library.

1. Choose Applications > CombiGlide > Reagent Preparation from the main window.

   The Reagent Preparation panel opens.

2. Click Browse.

   A file selector opens.

3. Select MDL SD from the Files of type option menu.
4. Select `acid_chlorides.sdf` from your working directory, and click Open.
5. Select SD property in the Create reagent titles from section and type `ReagentCode` into the text box.

   The ReagentCode property from the SD file will be used for the reagent title. Reagent titles are used for identification in CombiGlide. If you do not set unique titles, the reagent preparation procedure assigns arbitrary unique titles; however, if you use a descriptive field for the title, it will be easier to understand the output. If the descriptive field occurs multiple times, the procedure adds a suffix such as `-1`, `-2`, and so on.
6. Click the Acid_Chloride_C_C button in the Functional group to identify section.

   Note that there is more than one copy of most functional groups. In each copy, a different bond is replaced during the build process. When you select a functional group, you are also selecting the bond that is replaced.

   The name of the button, displayed in the tooltip, encodes the functional group, the fragment that will be kept and the fragment that will be discarded in the build process. The name of the functional group is Acid_Chloride (acid chloride). The two C's at the end of the name define the atoms on either side of the bond that is replaced in the build process: the first is the atom in the fragment that is kept, and the second is the atom in the fragment that is discarded. In this case, the C atom of the –COCl group is discarded, and the C atom of the R group is kept. Thus, what is attached to the core is just the R group. For more information on the functional group definitions, see Section 5.2.2 of the *CombiGlide User Manual*.
7. Click Start.

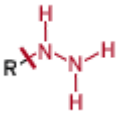
   The Start dialog box opens. This dialog box allows you to adjust job settings, such as selecting a host and a job name. For this exercise, you can use the defaults.
8. Click Start in the Start dialog box.

   The Monitor panel opens automatically and shows the progress of the reagent preparation process. The job is finished when the Status changes to incorporated : finished.

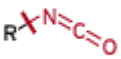
   A number of files, named `cg_acid_chlorides_Acid_Cl_C_C*`, are written to your working directory. The `cg_acid_chlorides_Acid_Cl_C_C.bld` file is the file used

by CombiGlide in the build process. Do not delete any of the reagent preparation files since many of them are used later in CombiGlide.

9. Repeat the reagent preparation process (Step 2 – Step 8) for the other two reagent files:
   - With `hydrazines.sdf` use the Hydrazine_C_N functional group.



   - With `isocyanates.sdf`, use the Isocyanate_C_N functional group.



   You do not need to wait for the first reagent preparation job to finish before you start the next job.

10. Close the Reagent Preparation panel.

You have now prepared all of the necessary reagent files. One of the reagents in the isocyanates input file contains an ionizable group and thus four structures are in the output file. The other two files should have three structures each. If you want to examine any of these files, you can import them into Maestro. When you open the Import panel, choose ReagentPrep from the Files of type option menu.

3.3 Importing the Core-Containing Molecule

To run CombiGlide, you must supply a molecule that contains the core structure. This molecule must be an all-atom, 3D structure that has a reasonable representation of the experimental geometry of the core structure. Ordinarily you would have to build or obtain this structure and minimize it using MacroModel or LigPrep, for example. For this tutorial, the core has already been built and minimized, and you only need to import it.

1. Click the Import structures button in the Maestro toolbar.

   The Import panel opens.

2. Ensure that Maestro is chosen from the Files of type option menu.

3. Select `core_tutorial.mae` and click Open.

   The 3D, minimized core-containing molecule is imported into the Project Table and displayed in the Workspace. You can close the Import panel now.

3.4 Defining the Reagent Combinations

Once you have a core-containing molecule and a set of reagents, you can start the combinatorial screening process. First, you must select the core-containing molecule, and determine which bonds in this structure will be replaced in the build process for each of the reagents. These are the *attachment positions*. In the pyrazole library example, the bonds to be replaced are marked in Figure 3.4.

1. Choose Applications > CombiGlide > Combinatorial Screening from the main window.

   The Combinatorial Screening panel opens with the Define Combinations step displayed and Pick Molecule selected.

2. Pick any atom in the core-containing molecule, which is displayed in the Workspace.

   The Core Molecule Title dialog box is displayed.

3. Type in a title and click OK.

The core-containing molecule is now defined. Next, you will define the attachment positions by clicking on the atoms of the bonds to be replaced in the build process. The bonds to be replaced are designated by numbers in Figure 3.4.

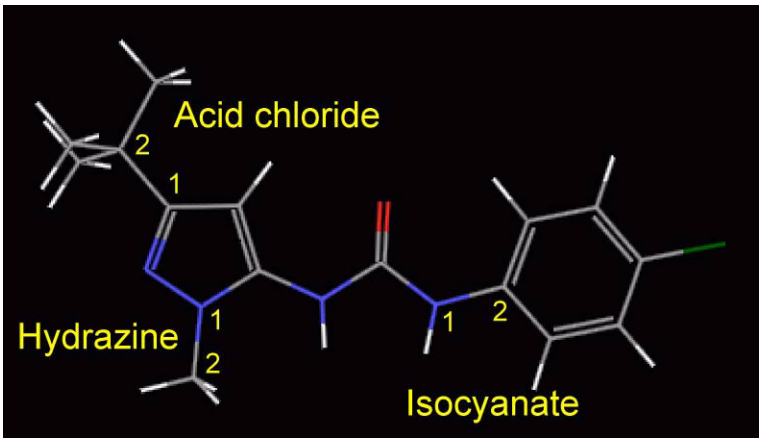


Figure 3.4. Attachment positions for the three reagents.

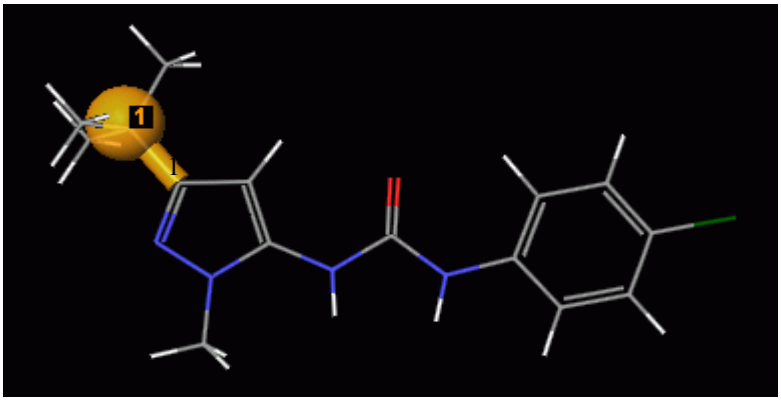


Figure 3.5. Attachment position for the acid chlorides after adding reagent file.

4. For the acid chloride bond, pick atom 1 then pick atom 2.

   A magenta cube appears around atom 1 when you pick it. After picking atom 2, a turquoise arrow pointing from atom 1 to atom 2 is displayed, labeled with the attachment position name, which is a number by default. The Select Reagent File panel opens.

5. Select the *reagent*`.bld` file to be associated with this attachment position and click OK.

   For the acid chloride position, this file is `cg_acid_chlorides_Acid_Cl_C_C.bld`.

   The attachment position and the reagent file name appear in the Attachments table along with the name of the functional group used to prepare the reagent file and the number of reagents in the file. (If multiple stereoisomers, ionization states, and tautomeric states were generated from the same molecule during reagent preparation, all of them are considered the same reagent and only counted once.)

   The arrow over the bond that will be replaced (the *attachment* bond) changes to a tube connecting to a sphere, colored gold, with the name associated with the position in the Attachments table still displayed. To rename the attachment, you can edit the table cell.

6. Repeat the above process (Step 4 and Step 5) to define the attachments for the hydrazine and isocyanate positions.

   If you make a mistake in the attachment position, select the table row and click Delete Attachment. You can then pick the correct atoms for the attachment position. If you make a mistake in the reagent file selection, select the table row and click Browse. You can then select the correct reagent file. When you select a table row, the attachment position is marked in turquoise in the Workspace.

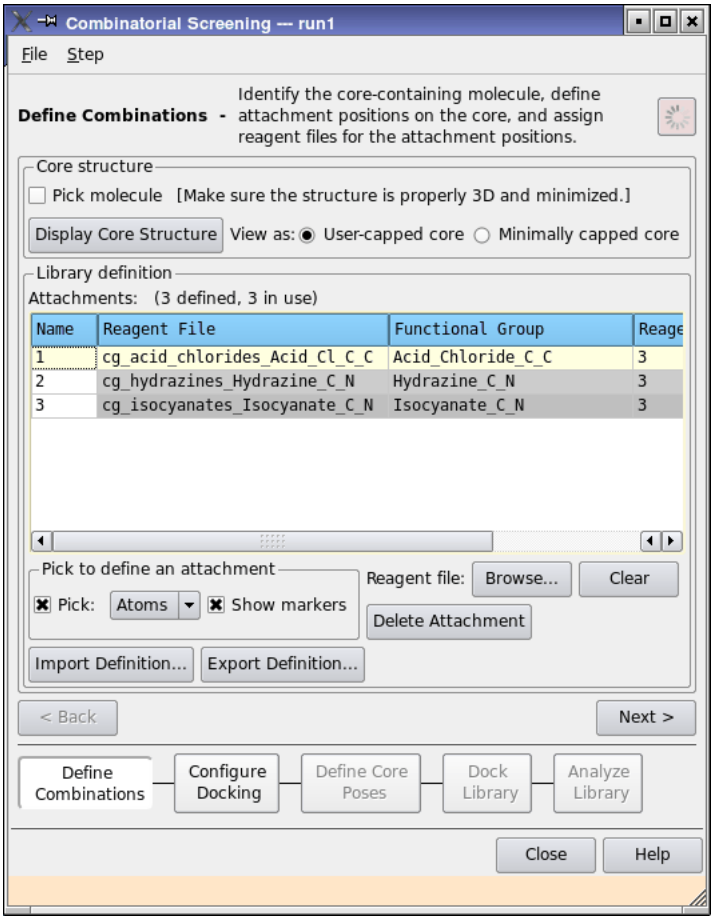


Figure 3.6. Define Combinations step after defining attachment positions.

The Name fields in the table can be edited. The default names are just consecutive numbers. You can consider naming the positions after the reagent libraries selected, using mnemonics such as AcCl for position 1, Hyd for position 2 and NCO for position 3. The names must be unique.

7. Click Export Definition.

   A file selector opens. Exporting the library definition is done here in preparation for the core hopping tutorial, which uses the same definitions. If you do not intend to do the core hopping tutorial, you can skip this step and the next step.

8. Enter `cg_tutorial` in the File name text box, and click Save.

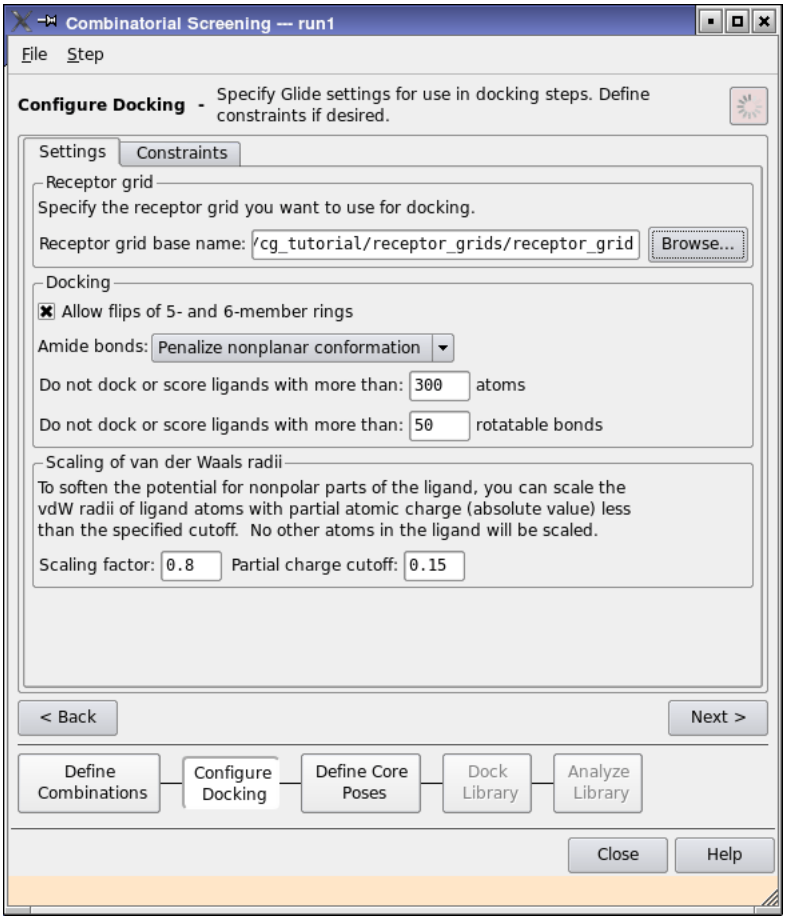


Figure 3.7. Configure Docking step after selecting the grid file.

9. Click Next.

   The Configure Docking step is displayed.

3.5 Configuring the Glide Docking Calculations

The next step is to configure the CombiGlide docking calculations. In a real application, you would select a receptor and generate the grids before starting the combinatorial screening process. You would then set up the parameters for the docking process in this step. For this tutorial, grids have already been generated.

1. In the Settings tab, click Browse in the Receptor grid section.

2. Navigate to the `receptor_grids` directory, select `receptor_grid.grd`, and click OK.

   The path to the grid files is displayed in the Receptor grid base name text box. We will be using the default docking settings in the tutorial, so no further settings need to be made.

3. Click Next.

   The Define Core Poses step is displayed.

3.6 Defining the Core Poses

In this tutorial, you will use the default settings for the docking of the core-containing molecule. The poses of the core-containing molecule are used as initial poses in the library docking.

The structure to be used in the core pose determination is the *user-capped core*, which should appear automatically in the Core structures table. The user-capped core is the core-containing molecule that you imported, with the original group at each attachment position. The molecule provided for the user-capped core in this tutorial has been docked into the frame of reference of the receptor. This is necessary when constraining to the position of the user-supplied core-containing molecule during the docking stage. For other choices, CombiGlide docks the core-containing molecule first.

An alternative is to use a minimally capped core, in which a minimal capping group is placed at each position. The minimal capping group is defined on page 52 of the *CombiGlide User Manual*. You can view the user-capped core by clicking the diamond in the In column for this molecule in the Core structures table.

1. Click Next.

   The Dock Library step is displayed.

3.7 Docking the Structures

You are now ready to start the docking phase of CombiGlide. In this phase, all possible structures generated by a single substitution at each attachment position are docked first ("single-position docking"), then a selection process is run on the results of this docking run to screen out poor poses, and finally a set of fully substituted structures is built and docked.

1. Click Dock.

   The Dock dialog box opens.

2. Under Docking task, ensure that Both single-position and combinatorial is selected.

This is the default. This choice runs the entire docking process: single-position docking, selection, and all-position docking. If you wish to view the results of the single-position docking runs before proceeding to docking the fully substituted structures, select Single position only. Once the single-position results are returned, you can perform the all-position docking by selecting Combinatorial only.

3. In the Single-position docking section, ensure that User-capped core is selected.
4. In the Combinatorial docking section, enter 32 in the Maximum number of structures to dock text box, and ensure that SP docking is selected.

   In the final stage of docking, CombiGlide will build and dock the structures that the selection algorithm considers to be the best, up to a maximum of 32 structures. The total number of structures that can be generated from the 3x3x3 library is 3x3x4 = 36 since one of the reagent files contained an ionizable group and therefore now contains four structures.

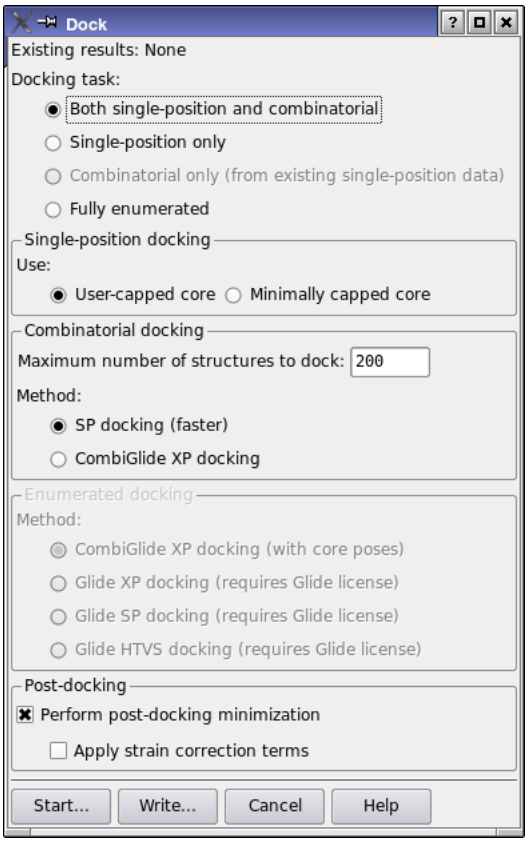


Figure 3.8. The Dock dialog box.

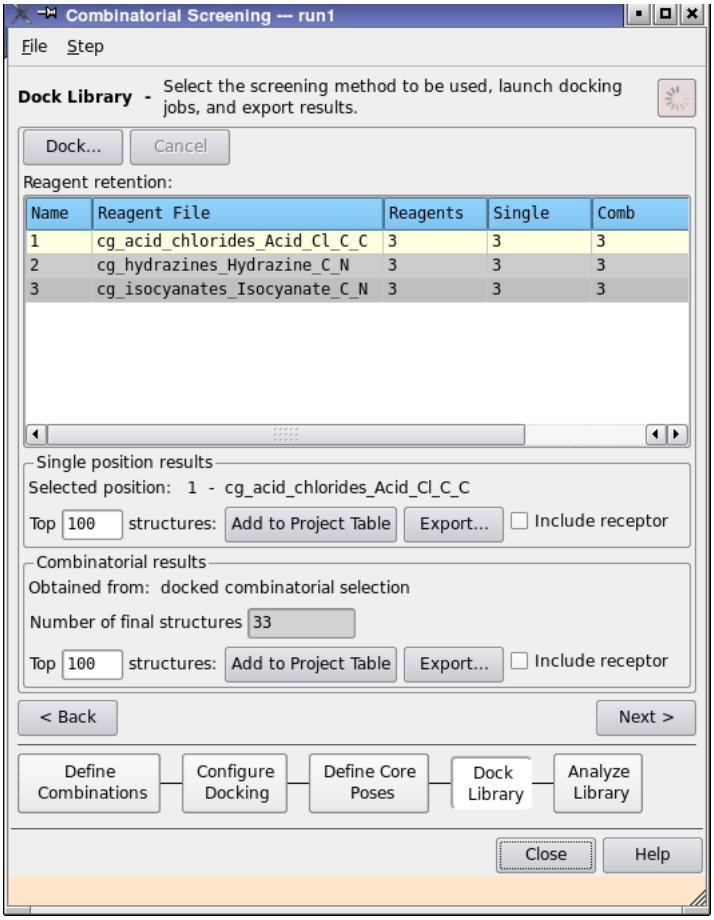


Figure 3.9. The Dock Library step after docking.

5. Click Start.

   The Start dialog box opens.

6. Select the host you wish to run the docking jobs on and distribute them as you see fit.

   For the tutorial, it is not necessary to separate the docking into subjobs since you are evaluating a small library. The overall docking process takes more than 1 hour on a 2 GHz processor.

7. Click Start.

   The jobs start and the job status button turns green and starts spinning, but the Monitor panel does not open. You can open the Monitor panel to monitor the docking jobs during the CombiGlide run by clicking the button.

   When all the jobs finish, the Single and Comb columns are populated in the Reagent retention table, and the total number of final docked structures is reported in the Number of final structures text box in the Combinatorial results section. Single is the number of reagents at the given position in the structures that were successfully docked in the single-position docking stage. Comb is the number of reagents at the given position in the structures that were successfully docked in the all-position docking stage. There should be 3 reagents in each column for each position.

   You can view the single-position results by selecting the row for the attachment position you wish to view in the Reagent retention table, then clicking Add to Project Table in the Single position results section of the panel. You can then view the structures using the Project Table. Note that more than one pose is saved for each reagent.

   To view the combinatorial results, click Add to Project Table in the Combinatorial results section. You can then view the structures using the Project Table.

8. Click Next.

   The Analyze Library step is displayed.

3.8 Analyzing the Library

When the docking jobs are finished, you can proceed to design the optimal focused combinatorial library based on the all-position docking results.

1. Click Filter and Select.

   The Filter and Select dialog box opens.

2. In the Selection Strategy folder, select Combinatorial and GlideScore.

3. Enter 24 into the Maximum library size text box.

4. Click OK.

   CombiGlide calculates the optimal combinatorial library using the GlideScore to determine the best reagents, with a maximum library size of 24. As can be seen in the Library column of the uppermost table in the panel, a 3x3x2 library (18 members) was generated.

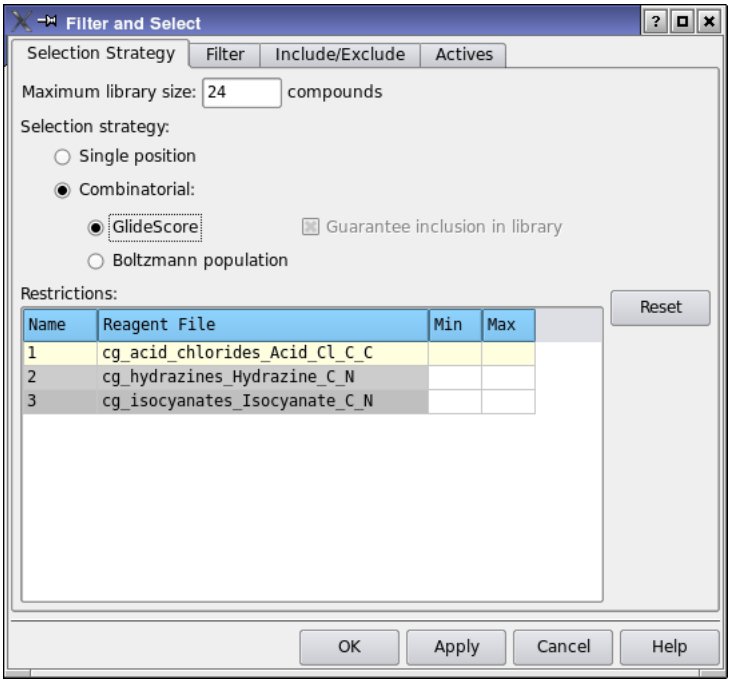


Figure 3.10. The Selection Strategy folder of the Filter and Select dialog box.

5. Click on the row for the attachment position associated with the isocyanate reagent file (Reagent Title: cg_isocyanates_Isocyanate_C_N).

   The data for this attachment position appear in the Reagents table. The rank 1 reagent is the reagent at that position for the best scoring structure from the all-position docking. The row for the rank 3 reagent is colored blue to indicate that the reagent was not selected for the library but was the reagent from the next best scoring structure from the all-position docking. This feature allows you to see the reagents that were close to being included in the focused library, and thus can help you to refine the library.

   To view the docked pose of the best-scoring structure containing a particular side chain, click on the square to the left of the reagent in the Reagents table.

6. Save the results of this library selection strategy by clicking Save and giving it the name `original`.

Next, you will filter the library using a set of properties, to further refine the library.

7. Click Filter and Select.
8. In the Filter folder, select Leadlike from the Filter set option menu.

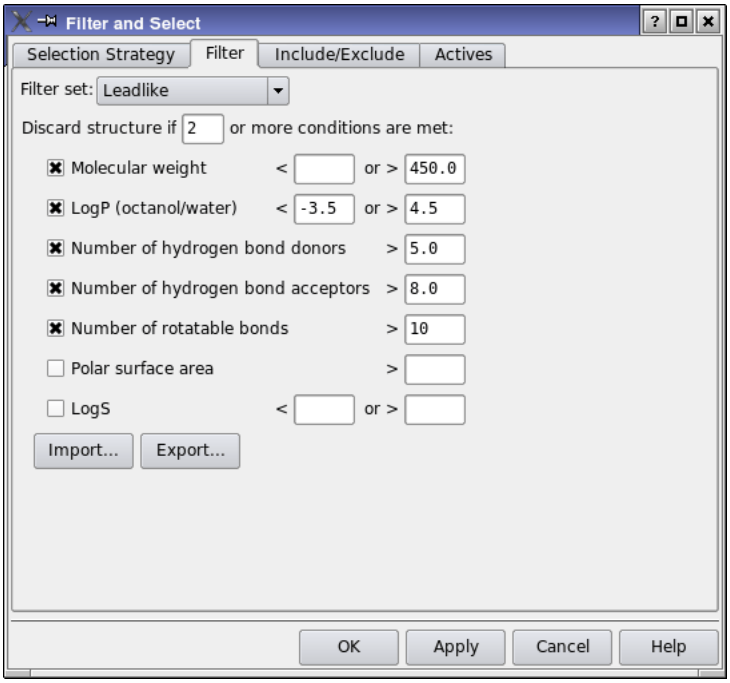


Figure 3.11. The Filter folder of the Filter and Select dialog box.

9. Click OK.

   This strategy adds a filter to the previous strategy, and returns a 3x3x2 library.

10. Save the results of this library selection strategy by clicking Save and giving it the name `leadlikefilter`.

To compare results from different strategies:

11. Click Compare in the Results section.

    The Compare Results dialog box opens.

12. Select original and leadlikefilter from the Select results to compare list.

13. Select 3 from the Position option menu.

    The reagents selected with both strategies appear in the panel for comparison. In this case there is no difference, because all reagents pass the leadlike filter.

To generate a text file summarizing the results of the current strategy, click Write Text File in the Results section of the Analyze Library step. The file contains the settings used in the strategy, the GlideScore ranges, and the list of reagents selected for each attachment position.

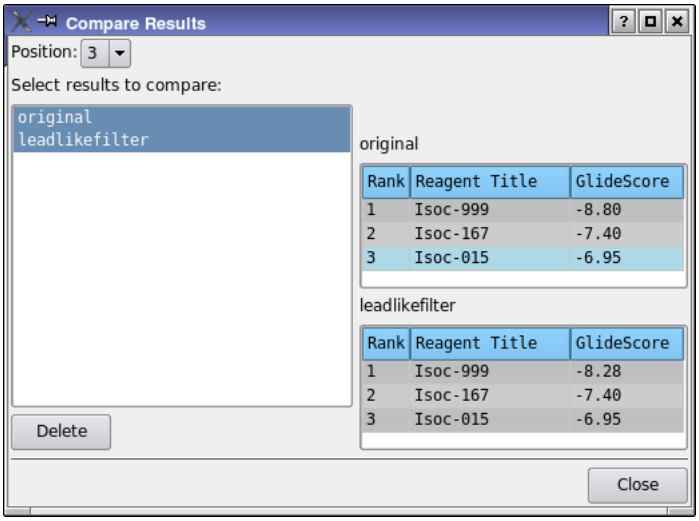


Figure 3.12. The Compare Results dialog box.

Once you select your final focused library, you can enumerate the entire library that can be prepared from the reagents chosen by your selection strategy, by clicking Create Library. By default, the structures in the library are untangled and minimized.

3.9 Changing Settings and Rerunning

There are occasions on which you may want to change some settings and rerun the calculations. You do not need to start from the beginning, but you can simply go back to the point where the settings need to be changed, and start from there. This section shows how to start from a point in the workflow. In this exercise, you will change the settings for the core poses.

1. Click the Define Core Poses button in the Guide.

   The Define Core Poses step is displayed.

2. Select Apply Glide core constraints.

   A warning dialog box is displayed, which allows you to choose whether to save the current results and create a new run, to proceed in the current run and delete the results that depend on this setting, or to cancel the change.

3. Select Save a copy before proceeding, and click OK.

   The default name for the new run is accepted (which should be `run2`). The old run is preserved, and the changes are made in the new run, which is now the current run. You can also save a run explicitly, by choosing Save As from the File menu.

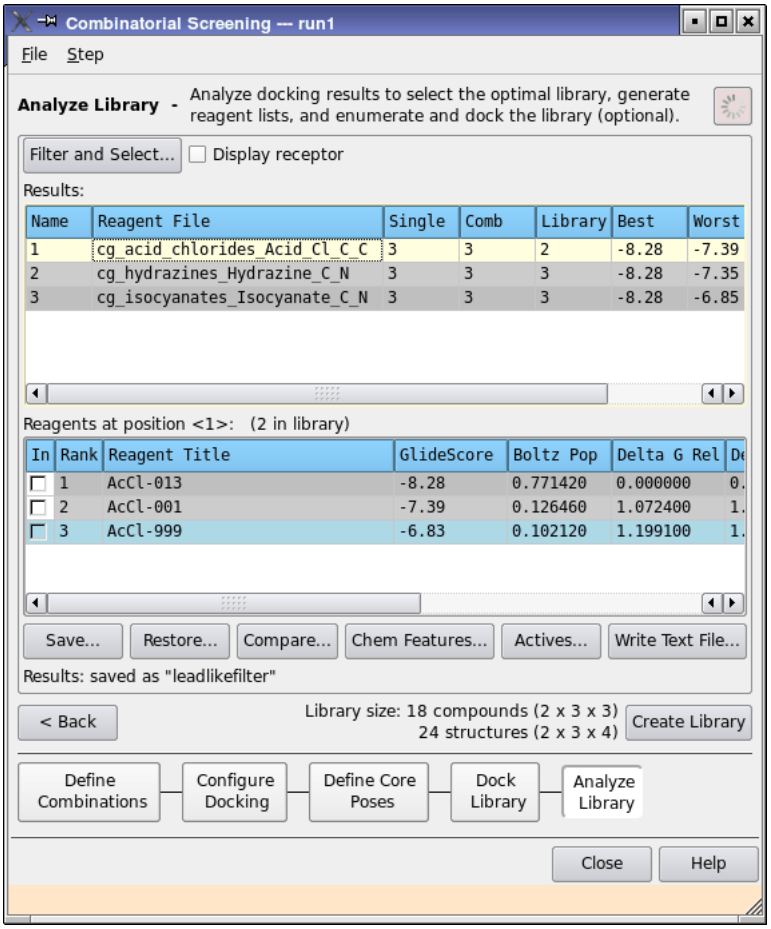


Figure 3.13. The Analyze Library step after analysis.

4. Proceed to the Dock Library step, by clicking the Guide button or Next.

You can now continue the tutorial from Section 3.7 on page 24. You might want to compare the results from run1 to those from run2, to examine the effect of core constraints.

Library Analysis

This chapter provides instruction on performing analysis of the chemical features in the library and of the enrichment of known actives. For a useful analysis, both of these tasks require a CombiGlide run that includes many more reagents for each attachment than we have used in the focused library design tutorial. Running the docking jobs to obtain the results is therefore impractical for the purposes of a tutorial. Instead, we provide results that you can analyze by running scripts from the command line. These scripts operate on the same files as are generated in a CombiGlide run, and display the same panels as are displayed from Maestro.

A detailed description of the interpretation of the features is given in Chapter 10 of the *CombiGlide User Manual*. Links to the manual material are provided so that you can read more on the interpretation of the panel displays.

If you have not already created a working directory and copied the tutorial files into it, do so now, using the instructions in Section 1.1 on page 1.

4.1 Chemical Features

The analysis of the chemical features in a library is done in Maestro with the Chemical Features panel. This panel can also be opened from the command line, which you will do in this tutorial. The system for which the data are provided is the same as for the virtual combinatorial screening tutorial, but with an expanded reagent set.

1. Change to your working directory:

   `cd` *workdir*

2. Run the following command to open the Chemical Features panel.

   ```
   $SCHRODINGER/utilities/cg_chem_features chem_features-rgnt.txt &
   ```

   This utility opens the file `chem_features-rgnt.txt` and uses it to generate the graphical data that are displayed in the panel. The file is generated by the program `libselector`. When you use the Filter & Select panel to run this program from Maestro, the file is stored inside the project.

   To open this panel from Maestro, you can click Chem Features in the Analyze Library step after performing a library selection in the Filter & Select panel.

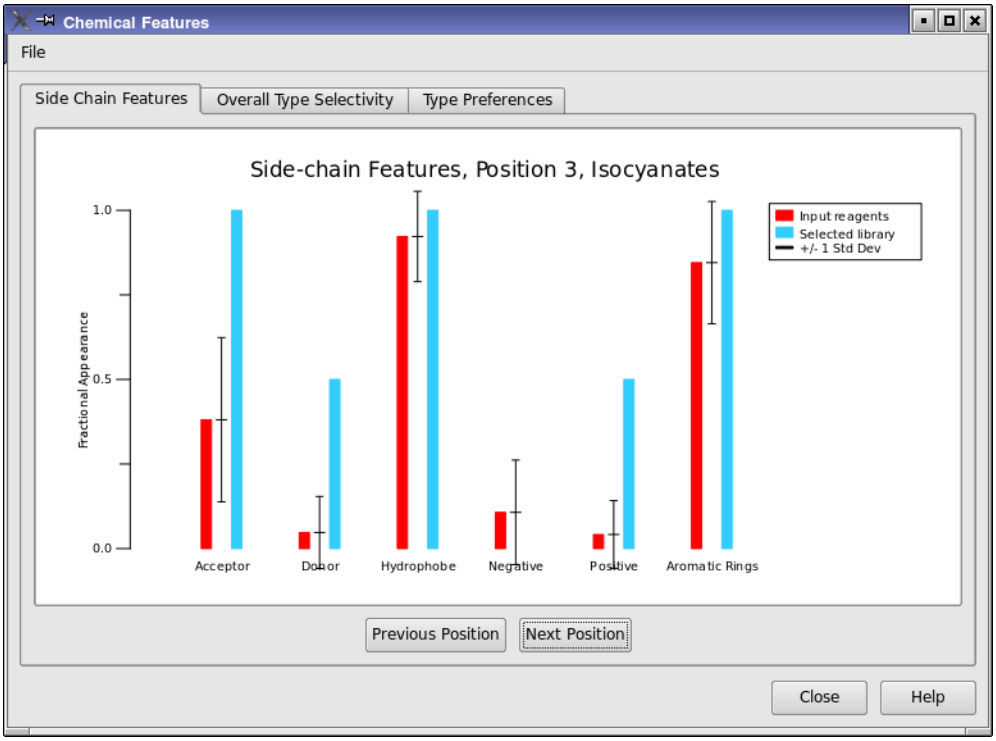


Figure 4.1. Chemical Features panel, showing Side Chain Features chart.

When you first open the panel, you will see a display headed Side-chain Features, Position 1, Acid_Chlorides. This heading refers to the type of display, which is selected by using the options at the top of the panel, and the attachment position, for which the position number and user-assigned name are both given. Below the chart are two buttons, which can be used to display the chart for other attachment positions.

The main purpose of the side-chain features chart is to examine the enrichment or depletion of chemical features in the selected library as compared to the full library (defined by the input reagent collection). The height of the blue bars relative to the red bars shows how much the feature is enriched (or depleted) in the selected library.

For the first position, there are significantly fewer acceptors in the selected library than in the input reagent collection. Donors and positive features have been eliminated, but the depletion is within the standard deviation, and is not statistically significant. To test whether this position selects against these features, you would have to supplement the reagent collection with compounds that contain these features.

Reagents without a hydrophobe have also been eliminated.

3. Click Next Position.

   This chart shows that there is no significant enrichment of any of the chemical feature types for the hydrazine reagent. However, reagents without an aromatic ring have been eliminated.

4. Click Next Position again.

   The third chart shows significant enrichment of acceptors, donors, and positive features at the isocyanate position. The core-containing structure in this case is the 1kv1 lead compound. In the more strongly binding 1kv2 ligand, BIRB796, the p-chlorophenyl substituent is replaced with one that contains donors, acceptors and positive centers as well as an aromatic ring. Thus, the chemical-feature information inferred by CombiGlide is consistent with the observed stronger binding of BIRB796. Note also that reagents that lack acceptors, donors, or hydrophobes have been eliminated: 100% of the reagents at this position in the selected library contain all these features.

The second kind of chart displays type selectivity. For background information, see Section 10.1.2.2 of the *CombiGlide User Manual*.

5. Select Overall Type Selectivity.

   The overall selectivity chart is displayed. It consists of vertical bars for each position that indicate how selective each position is for side-chain types. (A "type" is defined by a combination of features, so there are many more than 6 possible types. See Section 10.1.1 of the *CombiGlide User Manual* for more information.)

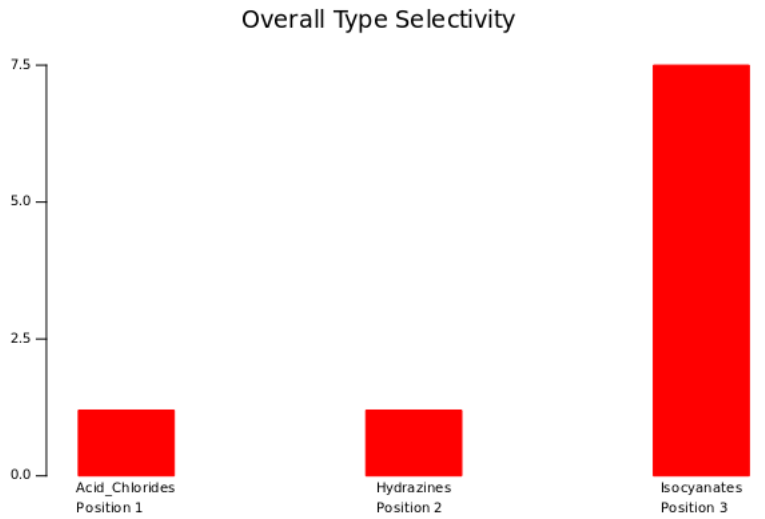


Figure 4.2. Overall type selectivity chart.

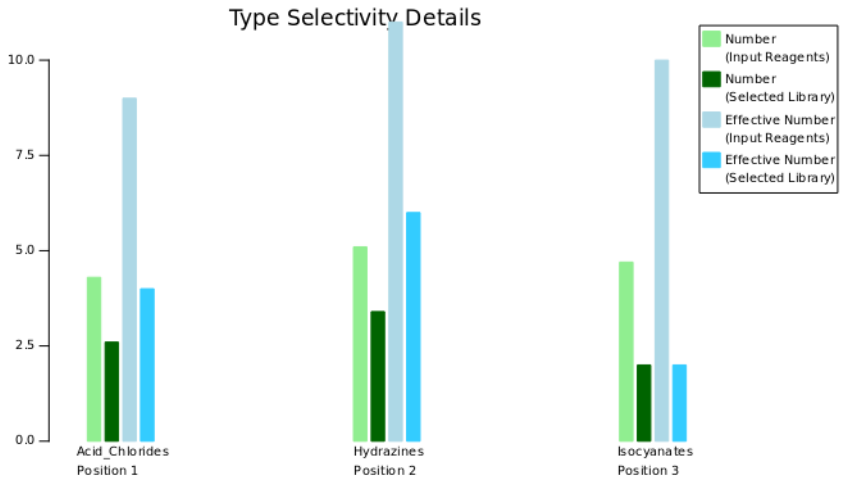


Figure 4.3. Type selectivity details chart.

The large value of 7 at position 3 indicates high selectivity, whereas the values of 1 at the other positions indicate low selectivity. Since selectivity is relative to the diversity of the reagent set, it is important to determine whether the low selectivities of positions 1 and 2 are due to lower diversity in their input reagent sets or to greater discrimination at position 3. This can be done by examining the type selectivity details.

6. Click Show Type Details.

   The Type Selectivity Details chart is displayed. The pale blue bars show the number of types in the input collection at each position. The numbers do not differ significantly between the positions, so on this basis the selectivity is not due to lower diversity at positions 1 and 2. The green bars show a diversity measure that takes into account the non-uniform distribution of types at a position. Again, there is not a significant variation in diversity between the three positions. The conclusion is that position 3 strongly discriminates between chemical types, but positions 1 and 2 do not.

   For more information on this display, see Section 10.1.2.2 of the *CombiGlide User Manual*.

Information on which types are enriched can be examined in the third chart type.

7. Select Type Preferences.

   The Type Preferences chart for position 3 is displayed. This was the last position displayed earlier. If for some reason this position is not displayed, click Next Position or Previous Position until it is.

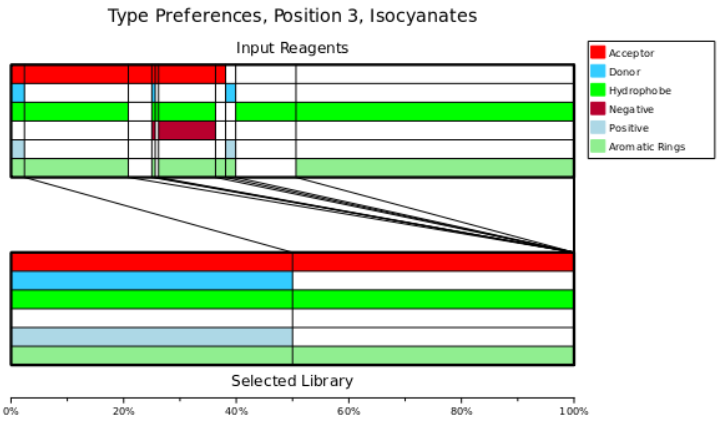


Figure 4.4. Type preferences plot.

Only two types (out of the ten that appear in the input collection) appear in the output, and these two types had rather low frequencies in the input collection. Both of these facts contribute to the high overall type selectivity exhibited by this position. The types that remain at this position all include an acceptor, a hydrophobe, and an aromatic ring, and lack a negative feature. The reagents that appear in the final collection each contain some of the features that exhibited significant enhancement in the Side Chain Features display.

8. Examine the chart for the other two positions, by clicking Previous Position or Next Position.

   Neither of these positions shows the same amount of selectivity, but both show the elimination of certain features.

Based on the results of this study, several possible directions for designing a better library might be pursued:

- Focus the reagent set at position 3 on the types that survived in the selected library. When this is done, the analysis will no longer show selectivity because the reagent set is no longer diverse. However, you will be able to explore reagents that are preselected to contain the features discriminated for and will therefore have a good chance of finding stronger binders.
- Check whether a hydrophobe is required at position 1 and an aromatic ring at position 2 by decreasing the proportion of reagents containing these features. The current statistics might be too small to judge whether the elimination of types containing these features is significant.

4.2 Enrichment of Actives

The analysis of the chemical features in a library is done in Maestro with the Actives panel. This panel can also be opened from the command line, which you will do in this tutorial.

1. Change to your working directory:

   `cd` *workdir*

2. Run the following command to open the Actives panel.

   ```
   $SCHRODINGER/utilities/cg_active_plot -r actives-rgnt.txt
   ```

   The Active Plot panel is displayed, with the data from the `actives-rgnt.txt` file plotted. This is the same panel as is displayed when you click Plot Enrichment Factors in the Actives panel, which in turn is opened by clicking Actives in the Analyze Library step of the Combinatorial Screening panel.

3. Select Log/Log Plot.

   The display is updated, and the plot should appear as shown in Figure 4.5.

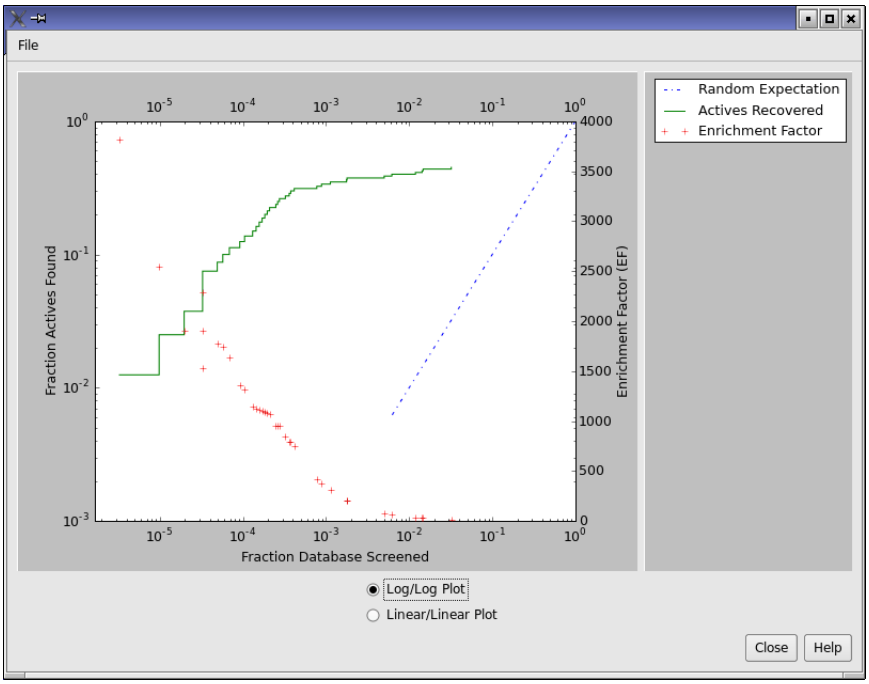


Figure 4.5. Enrichment factor plot.

The blue stepped line displays a standard enrichment curve of the fraction of actives found against the fraction of the database screened. The axes for this curve are displayed on the left and the bottom of the plot area. The fact that all points on this curve appear above the dashed line displaying the random expectation shows that the enrichment factor is everywhere greater than unity.

For each active found, the enrichment factor is denoted by the red crosses and read off the vertical axis on the right. Overall, this plot shows that early enrichments are in the thousands and that enrichment factor decreases, as expected, as more of the library is screened.

The top horizontal axis shows the library sizes corresponding to the values of the fraction of the database screened. This plot shows that the selected 1000-compound combinatorial library exhibits an enrichment factor of about 500, meaning that it contains 500 times more active compounds than a random selection of 1000 compounds is expected to have.

Getting Help

Schrödinger software is distributed with documentation in PDF format. If the documentation is not installed in `$SCHRODINGER/docs` on a computer that you have access to, you should install it or ask your system administrator to install it.

For help installing and setting up licenses for Schrödinger software and installing documentation, see the *Installation Guide*. For information on running jobs, see the *Job Control Guide*.

Maestro has automatic, context-sensitive help (Auto-Help and Balloon Help, or tooltips), and an online help system. To get help, follow the steps below.

- Check the Auto-Help text box, which is located at the foot of the main window. If help is available for the task you are performing, it is automatically displayed there. Auto-Help contains a single line of information. For more detailed information, use the online help.
- If you want information about a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Maestro menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- For information about a panel or the tab that is displayed in a panel, click the Help button in the panel, or press F1. The help topic is displayed in your browser.
- For other information in the online help, open the default help topic by choosing Online Help from the Help menu on the main menu bar or by pressing CTRL+H. This topic is displayed in your browser. You can navigate to topics in the navigation bar.

The Help menu also provides access to the manuals (including a full text search), the FAQ pages, the New Features pages, and several other topics.

If you do not find the information you need in the Maestro help system, check the following sources:

- *Maestro User Manual*, for detailed information on using Maestro
- *Maestro Command Reference Manual*, for information on Maestro commands
- *Maestro Overview*, for an overview of the main features of Maestro
- *Maestro Tutorial*, for a tutorial introduction to basic Maestro features
- *CombiGlide User Manual*, for detailed information on using CombiGlide
- *Glide User Manual*, for detailed information on using Glide

- CombiGlide Frequently Asked Questions pages, at https://www.schrodinger.com/CombiGlide_FAQ.html
- Known Issues pages, available on the Support Center.

The manuals are also available in PDF format from the Schrödinger Support Center. Local copies of the FAQs and Known Issues pages can be viewed by opening the file `Suite_2009_Index.html`, which is in the `docs` directory of the software installation, and following the links to the relevant index pages.

Information on available scripts can be found on the Script Center. Information on available software updates can be obtained by choosing Check for Updates from the Maestro menu.

If you have questions that are not answered from any of the above sources, contact Schrödinger using the information below.

E-mail: help@schrodinger.com
USPS: Schrödinger, 101 SW Main Street, Suite 1300, Portland, OR 97204
Phone: (503) 299-1150
Fax: (503) 299-4532
WWW: http://www.schrodinger.com
FTP: ftp://ftp.schrodinger.com

Generally, e-mail correspondence is best because you can send machine output, if necessary. When sending e-mail messages, please include the following information:

- All relevant user input and machine output
- CombiGlide purchaser (company, research institution, or individual)
- Primary CombiGlide user
- Computer platform type
- Operating system with version number
- CombiGlide version number
- Maestro version number
- mmshare version number

On UNIX you can obtain the machine and system information listed above by entering the following command at a shell prompt:

```
$SCHRODINGER/utilities/postmortem
```

This command generates a file named *username*`-`*host*`-schrodinger.tar.gz`, which you should send to help@schrodinger.com. If you have a job that failed, enter the following command:

```
$SCHRODINGER/utilities/postmortem jobid
```

where *jobid* is the job ID of the failed job, which you can find in the Monitor panel. This command archives job information as well as the machine and system information, and includes input and output files (but not structure files). If you have sensitive data in the job launch directory, you should move those files to another location first. The archive is named *jobid*`-archive.tar.gz`, and should be sent to help@schrodinger.com instead.

If Maestro fails, an error report that contains the relevant information is written to the current working directory. The report is named `maestro_error.txt`, and should be sent to help@schrodinger.com. A message giving the location of this file is written to the terminal window.

More information on the `postmortem` command can be found in Appendix A of the *Job Control Guide*.

On Windows, machine and system information is stored on your desktop in the file `schrodinger_machid.txt`. If you have installed software versions for more than one release, there will be multiple copies of this file, named `schrodinger_machid-`*N*`.txt`, where *N* is a number. In this case you should check that you send the correct version of the file (which will usually be the latest version).

If Maestro fails to start, send email to help@schrodinger.com describing the circumstances, and attach the file `maestro_error.txt`. If Maestro fails after startup, attach this file and the file `maestro.EXE.dmp`. These files can be found in the following directory:

```
%USERPROFILE%\Local Settings\Application Data\Schrodinger\appcrash
```

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